

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of
Bakel Van et al

Atty. Ref.: 101384-1 US

Serial No. 10/518, 164

Art Unit 1625

Filed: July 25, 2005

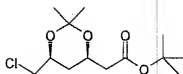
Examiner: Taylor Victor Oh

For: PROCESS FOR THE PREPARATION OF DIOXANE ACETIC ACID
ESTERS

DECLARATION

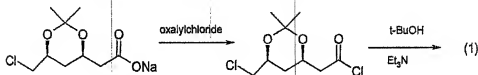
I, Dominique Monique Charles Callant of De Huttestraat 87, 3530 Houthalen,
Belgium hereby declare as follows:

1. I am a chemist with eighteen years experience in Research & Development for fine chemical synthesis, in particular scale-up and development. I am employed by DSM, a major Life Science and Materials Science company, with centres all over the world including The Netherlands as Senior Scientist.
2. I am aware of the content of the present patent application and have reviewed the content of the claims currently on the file at the US Patent and Trade Mark Office. I have also read the office action dated January 16, 2008 and in particular the objections set out on pages 3 and 4 of that action.
3. Within DSM, statol, a compound of formula (I)



(1)

was produced as an intermediate for a cholesterol-lowering drug (Rosuvastatin). The compound had generally been produced by a route that may be summarised as follows:



Specifically, in the final step, the corresponding chloro derivative was reacted with tert-butanol in the presence of triethylamine as a base. Yields of the desired product using in this route were in the range of from 40-90%.

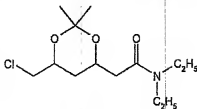
4. In 2001, a series of experiments were carried out under my direct supervision, in collaboration with my co-inventor, Peter Johannes Dominicus Maas* to determine the relative merits of triethylamine (Et_3N) and N-methyl-morpholine (NMM) as a base in the final step. The reactions were carried out as described in Example 2 of the US Serial No. 10/518, 164. Specifically, in a 100 ml HEL vessel with 4 blade stirrer 8.0 g (4R-cis)-(6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetic acid, sodium salt (92.4%; 30 mmol) was suspended in 41 g toluene and 0.3 g NMP (3 mmol). Over a period of 1 hour, 4.5 g (36 mmol) oxalylchloride was dosed at a temperature of 15-20°C. The reaction mixture (50 g) was stirred for 2.5 hours. The reaction mixture was split into 2 parts: Part A (23.83 g) and part B (24.25 g). Part A of the reaction mixture was dosed over a period of 1 hour to a mixture of 22.2 g (20 eq.) t-butanol and 3.0 g (2 eq.) NMM at 25°C. The reaction mixture was stirred overnight and analyzed by GC. The yield of the t-butyl ester of formula (1) was 88% as reported in US Serial No. 10/518,165.

Part B of the reaction mixture was dosed during 1 h. to a mixture of 22.2 g (20 eq.) t-butanol and 3.0 g (2 eq.) Et_3N at 25°C . The reaction mixture was stirred overnight and analyzed by GC. The yield of the t-butyl ester was 41%.

5. The experiment was repeated with each base and different amounts of oxalyl chloride and different amounts of base at either 10°C . In one case, the reaction was effected with dipped dosing. The results are summarised in the following Table.

Oxalyl chloride	Conc	Temp	Dose time	Amount base	Amount tert-BuOH	dipped dosing	Yield with Et_3N	Yield with NMM
eq	m-%	$^\circ\text{C}$	hour	eq	eq	Y/N	mol%	mol%
1.2	10	10	1	5.0	20	N	60.6	85.1
1.2	10	10	1	2.5	20	N	68.1	94.7
1.6	10	10	1	5.0	20	N	86.8	101.6
1.6	10	10	1	2.5	20	N	88.9	98.0
1.4	16	15-20	1	2.0	13	N	89.0	97.3
1.4	16	15-20	1	2.0	13	Y	89.5	93.0

6. It is clear from these results that the yields when NMM is used as a base are consistently better than when Et_3N is used. These results were unexpected and so the reason for this difference was investigated further. It appeared that when Et_3N was used, we noted a significant amount of a bi-product of formula (2)



(2)

was being produced. In this case therefore, it the bases were not equivalent in the reaction.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.



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Dominique Monique Charles Callant

May 5, 2008
Date